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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,984	03/15/2004	Nirmal Mulye	14276	2376

23389 7590 10/28/2008

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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,984	MULYE, NIRMAL	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 38, 40 -70* is/are pending in the application.

4a) Of the above claim(s) *1 - 37, 49 - 53, 57, 58, 61, 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, 40 - 48, 54 - 56, 59, 60, 63 - 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed July 30, 2008, have been fully considered.

Response to Amendment

1. The declaration filed on July 30, 2008 under 37 CFR 1.131 is sufficient to overcome the Tyebji et al. (WO 03/026637) reference.

2. Applicant's arguments with respect to the double patenting rejection and the rejection under 35 USC 103(a) have been considered but are moot in view of the disqualification of the Tyebji et al. (WO 03/026637) by the Rule 1.131 affidavit and the new ground(s) of rejection applied below.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 38, 40 –46, 47, 54 – 56, 59, 60 and 63 – 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shell et al. (US 6,340,475) in view of Grillo et al. (WO 91/15548).

Shell et al. discloses sustained or controlled release dosage forms which contain polymeric material which swell upon contact with water (abstract). Highly water soluble drugs can be administered in a sustained release form because this swelling retains the dosage form in the stomach and retards diffusion (col 6, ln 18 – 23). Suitable polymers include cellulose polymers and their derivatives, microcrystalline cellulose and xanthan gum (col 7, ln 54 – 64). Particularly preferred cellulosic polymers include hydroxypropylmethylcellulose (col 8, ln 8 – 17). These polymers can be used individually or in combination and certain combinations often provide a more controlled release of the drug than the individual counterparts (col 9, ln 42 – 49). The formulations can take the form of particles, tablets and particles retained in capsules (col 9, ln 61 – 62).

In example 4 (beginning at col 13, ln 65), metformin controlled release dosage forms with various polymers and combinations of polymers are prepared, including xanthan gum only, HPMC only, hydroxyethylcellulose and polyethylene oxide (PEO) combination (ratio approximately 12.5:1) and a combination of xanthan gum and a starch graft polymer combination (ratio approximately 1:9). The lubricant magnesium

stearate is also included in the various formulations. As shown in figure 4, each composition displays a slightly different release profile. In example 10, a metformin dosage from comprising metformin, PEO, magnesium stearate and the HPMC containing OPADRY® Clear coating is applied (col 17, ln 26 – 34).

Shell et al. does not disclose the inclusion of maltodextrin in the pharmaceutical formulation.

Grillo et al. discloses a method of coating substrates such as pharmaceutical tablets with a protective film which comprises a mixture of a cellulosic polymer, maltodextrin and a plasticizer (abstract). For pharmaceutical tablets, a coated tablet is easier to swallow and can mask the taste of the active ingredient (p 15, ln 16 – 19). A colorant can also be added to provide the finished product with a color (p 19, ln 10 – 11). The inclusion of the low molecular weight maltodextrin with the higher molecular weight cellulosic polymer enables clearer films with high tensile strength to be applied (p 2, ln 19 – p 3, ln 17). Preferably, the weight ratio of the maltodextrin to the cellulosic polymer(s) is 3:7, although good coatings can be obtained with the percentage of maltodextrin being between 5% and 95% by weight of the cellulosic polymer (p 6, ln 1 – 12).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a sustained release metformin dosage form comprising a sustained release matrix material such as xanthan gum, a cellulosic polymer such as microcrystalline cellulose, active ingredient and lubricant as taught by Shell et al. and to coat the tablet with the maltodextrin coating composition with improved properties of

clarity and tensile strength as taught by Grillo et al. The amount of the various ingredients is a results effective parameter that one of ordinary skill in the art would routinely optimize. For example, if HPMC is used in both the coating and as part of the sustained release matrix, the ratio of cellulosic polymer to the maltodextrin would be different than a composition in which HPMC was only present in the coating and either a different cellulosic polymer or a non-cellulosic polymer such as xanthan gum or PEO was used as the sustained release material. Also, altering the relative amounts of the various polymers used as the sustained release material will affect the release rate of the active ingredient.

6. Claims 38, 40 – 44, 46 – 48, 54 – 56, 59, 60 and 63 – 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shell et al. and Grillo et al. (WO 91/15548) as applied to claims 38, 40 – 44, 46, 47, 54 – 56, 59, 60 and 63 – 66 above, and further in view of Tobyn et al. (Intl J Pharm 1998).

As discussed above, Shell et al. and Grillo et al. disclose a sustained release formulation of drugs such as metformin that can comprise a polymer or mixture of polymers as the sustained release matrix material, including a cellulosic polymer and a lubricant coated with a cellulosic polymer/maltodextrin coating.

Neither reference discloses the use of silicified microcrystalline cellulose (SMCC).

Tobyn et al. discloses the MCC is widely used as a filler and binder for wet granulation, direct compression tabletting and a filler for hard gelatin capsules (p 183,

col 1, ¶1) and it has been rated as the most useful filler for direct compression tabletting (p 183, col 2, ¶1). While MCC is very useful, SMCC possesses a number of advantages in terms of powder flow, tablet strength, lubricant sensitivity and wet granulation (p 184, col 2, ¶ 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to add either MCC or SMCC, which exhibits improved behavior in comparison to MCC, to the tablet formulation disclosed by Shell et al. and Grillo et al., as the inclusion of this excipient is taught by Tobyn et al. to be useful in the tabletting process.

7. Claims 38, 40 – 43, 46 – 48, 54 – 56, 59, 60 and 63 – 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mulye et al. (US 6,416,786) in view of Grillo et al. (WO 91/15548).

Mulye et al. discloses a solid sustained release tablet comprising a hydrocolloid such as xanthan gum and a cellulose ether as the sustained release carrier (abstract). A variety of active ingredients can be included in the sustained release formulation (col 3, ln 65 – col 4, ln 25). The amount of hydrocolloid and cellulose ether present are preferably between about 1:0.01 to about 1:2, or more preferably 1:0.05 to about 1:0.4 (col 6, ln 37 – 41). Hydroxypropylmethylcellulose in various forms are disclosed as suitable for the cellulose ether fraction of the sustained release carrier (col 4, ln 44 – 67). A lubricant may be added to avoid tablet sticking (col 6, ln 64 – 66). A filler such as the pharmaceutically acceptable saccharide microcrystalline cellulose can also be

included (col 7, ln 3 – 17) and the tablets can be coated (col 8, ln 43 – 45). In example 1 (col 9, ln 57 – 63), niacin, xanthan gum (XG), HPMC, SMCC and talc are made into tablets. The ratio of XG:HPMC is 1:0.5. The other non-comparative examples make use of xanthan gum and HPMC with SMCC, although the ratio of XG:HPMC varies.

Mulye et al. does not disclose the use of maltodextrin in the formulations.

Grillo et al. discloses a method of coating substrates such as pharmaceutical tablets with a protective film which comprises a mixture of a cellulosic polymer, maltodextrin and a plasticizer (abstract). For pharmaceutical tablets, a coated tablet is easier to swallow and can mask the taste of the active ingredient (p 15, ln 16 – 19). A colorant can also be added to provide the finished pharmaceutical with a color (p 19, ln 10 – 11). The inclusion of the low molecular weight maltodextrin with the higher molecular weight cellulosic polymer enables clearer films with high tensile strength to be applied (p 2, ln 19 – p 3, ln 17). Preferably, the weight ratio of the maltodextrin to the cellulosic polymer(s) is 3:7, although good coatings can be obtained with the percentage of maltodextrin being between 5% and 95% by weight of the cellulosic polymer (p 6, ln 1 – 12).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a sustained release dosage form comprising a sustained release matrix material such as xanthan gum, HPMC, SMCC, active ingredient and lubricant as taught by Mulye et al. and to coat the tablet with the maltodextrin coating composition with improved properties of clarity and tensile strength as taught by Grillo et

al. The ratios of XG to HPMC disclosed by Mulye et al. fall within the ranges claimed by Applicant.

8. Claims 38, 40 – 48, 54 – 56, 59, 60 and 63 – 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mulye et al. and Grillo et al. as applied to claims 38, 40 – 44, 46 – 48, 54 – 56, 59, 60 and 63 – 70 above further in view of Kumar (US 6,117,451).

Mulye et al. and Grillo et al. disclose a sustained release dosage form comprising xanthan gum, HPMC, SMCC which can be coated with a cellulosic polymer/maltodextrin coating to improve the characteristics of the tablet.

Neither reference disclosed metformin as an active ingredient in the sustained release tablet formulations.

Kumar discloses metformin hydrochloride tablets with excipients to enhance the tabletting mix (abstract). HPMC controls drug release from solid dosage forms (col 4, ln 24 – 28). Various grade of this polymer with different rates of hydration are available which influence the release rate of the metformin (col 8, ln 51 – 61).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare the sustained release formulation taught by Mulye et al. and Grillo et al. and to use metformin as the active ingredient in the sustained release dosage form, as taught by Kumar, to prepare a metformin containing dosage form.

9. Claims 38, 40 – 47, 54 – 56, 59, 60 and 63 – 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US 6,120,803).

Wong et al. discloses a dosage form adapted for retention in the stomach that is useful for prolonged (sustained) delivery of the active ingredient (abstract). In one embodiment, the dosage form comprises an active agent, a polymer matrix which is a mixture of a high molecular weight, water-soluble polymer and a hydroattractatct such as a water insoluble polymer, optional non-polymer water-soluble excipients and a band of insoluble material (col 5, ln 43 – 54). The polymer can be a single polymer or a mixture of different polymers (col 9, ln 19 – 20). Examples of water soluble polymers given include HPMC, maltodextrin and xanthan gum (col 5, ln 55 – 63). Examples of hydroattractants include hydroxyproplycellulose and MCC (col 6, ln 3 – 5). While maltodextrin can be used a water soluble polymer in the swellable polymer matrix, maltodextrin can also be added as low molecular weight polymeric material (col 6, ln 27 - 30) that can be included to serve useful functions in tablet formation such as increased active ingredient stability or tablet compression (col 21, ln 7 – 11). Among the active ingredients indicated as suitable for inclusion in this dosage form is metformin (col 18, ln 27). In examples 7 and 8 (beginning at col 26, ln 13), dosage forms comprising a polymer matrix of PEO and hydroxypropyl cellulose and the lubricant magnesium stearate are prepared that is coated with a film coating comprising methyl cellulose and sorbitol. While PEO is used as the water-soluble component of the polymer matrix in preparation 1 (col 22), the functionally equivalent HPMC is used in place of the PEO in

example 3 (col 25). Hydroxypropylcelluose is used as the hydroattractant in preparation 1, the functionally equivalent MCC is used as the hydroattractant in example 4 (col 25).

Wong et al. does not explicitly prepare a sustained release composition comprising maltodextrin and the other elements as required in claim 38.

It would have been obvious to one of ordinary skill in the art to prepare a coated, sustained release dosage device including an active ingredient such as metformin as taught by Wong et al. and to use a water-soluble polymer such as maltodextrin and HPMC or xanthan gum and a hydroattractant such as MCC as the sustained release dosage form as the various elements are presented in the specification as functional equivalents to those which are presented in the examples and explicitly disclosed.

10. Claims 38, 40 – 48, 54 – 56, 59, 60 and 63 – 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. as applied to claims 38, 40 – 47, 54 – 56, 59, 60 and 63 – 66 above, and further in view of Tobyn et al. (Intl J Pharm 1998).

Wong et al. discloses an optionally coated sustained release dosage form comprising an active ingredient and a polymer matrix comprised of a high molecular weight, water soluble polymer such as maltodextrin, xanthan gum, and/or HPMC and a hydroattractant such as microcrystalline cellulose.

Wong et al. does not disclose the use of sillicified MCC (SMCC).

Tobyn et al. discloses the MCC is widely used as a filler and binder for wet granulation, direct compression tabletting and a filler for hard gelatin capsules (p 183,

col 1, ¶1) and it has been rated as the most useful filler for direct compression tabletting (p 183, col 2, ¶1). While MCC is very useful, SMCC possesses a number of advantages in terms of powder flow, tablet strength, lubricant sensitivity and wet granulation (p 184, col 2, ¶ 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use SMCC which exhibits improved behavior in comparison to MCC inplace of the MCC in the tablet formulation disclosed by Wong et al.

11. Claims 38, 40 – 48, 54 – 56, 59, 60 and 63 – 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. as applied to claims 38, 40 – 47, 54 – 56, 59, 60 and 63 – 66 above, and further in view of Grillo et al. (WO 91/15548).

Wong et al. discloses an optionally coated sustained release dosage form comprising an active ingredient and a polymer matrix comprised of a high molecular weight, water soluble polymer such as maltodextrin, xanthan gum, and/or HPMC and a hydroattractant such as microcrystalline cellulose.

Wong et al. does not explicitly disclose the use of maltodextrin in the formulation.

Grillo et al. discloses a method of coating substrates such as pharmaceutical tablets with a protective film which comprises a mixture of a cellulosic polymer, maltodextrin and a plasticizer (abstract). For pharmaceutical tablets, a coated tablet is easier to swallow and can mask the taste of the active ingredient (p 15, ln 16 – 19). A colorant can also be added to provide the finished product with a color (p 19, ln 10 – 11). The inclusion of the low molecular weight maltodextrin with the higher molecular

weight cellulosic polymer enables clearer films with high tensile strength to be applied (p 2, ln 19 – p 3, ln 17). Preferably, the weight ratio of the maltodextrin to the cellulosic polymer(s) is 3:7, although good coatings can be obtained with the percentage of maltodextrin being between 5% and 95% by weight of the cellulosic polymer (p 6, ln 1 – 12).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a sustained release dosage form as taught by Wong et al. and to coat the pharmaceutical formulation with the improved tensile strength while remaining clear coating formulation taught by Grillo et al. Therefore, even if maltodextrin is not selected as the sole or part of the water soluble polymer in the dosage form of Wong et al., the pharmaceutical formulation could contain maltodextrin as part of the formulation but in the coating, not the core of the dosage form. The amount of the various ingredients is a results effective parameter that one of ordinary skill in the art would routinely optimize. For example, if HPMC is used in both the coating and as part of the sustained release matrix, the ratio of cellulosic polymer to the maltodextrin would be different than a composition in which HPMC was only present in the coating and either a different cellulosic polymer or a non-cellulosic polymer such as xanthan gum or PEO was used as the sustained release material.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

NMW